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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,969	06/17/1999	BENT KARSTEN JAKOBSEN	102286.410	5926
7590 12/19/2003 HOLLIE L BAKER HALE AND DORR LLP 60 STATE STREET BOSTON, MA 02109			EXAMINER DIBRINO, MARIANNE NMN	
			ART UNIT 1644	PAPER NUMBER

DATE MAILED: 12/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/334,969

Applicant(s)

JAKOBSEN ET AL.

Examiner

DiBrino Marianne

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 28 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-11, 14<sup>21</sup> and 33-36 is/are pending in the application.
- 4a) Of the above claim(s) 33 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-11, 14-27 and 34-36 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☒ None of:  
1. ☒ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.  
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_. 6) ☐ Other: \_\_\_\_\_

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### DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/28/03 has been entered.

2. Applicant's amendment filed 7/28/03 is acknowledged and has been entered.

3. The numbering of claims is not accordance with 37 C.F.R. 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When claims are added, except when presented in accordance with 37 CFR 1.121(b), they must be renumbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 33-35 have been renumbered as claims 34-36.

It is noted by the Examiner that non-elected claim 33 is pending.

4. Applicant is reminded of Applicant's election without traverse of Group I (claims 1-27), and species of the specific complex of a TCR tetramer comprising four  $\alpha\beta$  dimers and the specific linker molecule of avidin in Paper No. 7.

Claims 1-11, 14-27 and 34-36 read on the elected species and are presently being examined.

5. The disclosure is objected to because of the following informality:

There is a spelling error on page 93, i.e., "R frenc s".

Appropriate correction is required.

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**In view of Applicant's amendment filed 7/28/03 the following grounds of rejection remain.**

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103<sup>©</sup> and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-11, 14-18, 26, 27 and 34-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99).

WO 97/35991 teaches soluble (i.e., extracellular domains) recombinant divalent and multivalent analogs (including tetravalent, i.e., a tetramer) of heterodimeric proteins and pharmaceutical compositions thereof, including  $\alpha\beta$  TCR that possess enhanced affinity for their target molecules, said  $\alpha\beta$  TCRs being associated via Ig linker molecules which may further comprise a toxin, i.e., a "cytotoxic agent" as recited in instant claim 26, and/or may be further linked by association via avidin (especially page 8, line 31, page 9, lines 1-4, page 10, lines 27-31, page 11, lines 1-7, page 14, lines 7-16, Figure 1D and legend, claims 1-5, 8, 10-14, 17, 27 and 28, page 1, lines 14-17, page 16, lines 1-14). With regard to instant claim 17, the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1). WO 97/35991 also teaches production of the multimers in baculovirus with a yield of about 1 ug/ml (i.e., about 1 mg/L). WO 97/35991 also teaches short flexible Gly-Ser spacers between the TCR chain and the Ig portion (Figure 1D and legend).

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WO 97/35991 does not teach multivalent soluble  $\alpha\beta$  TCR wherein each chain has a heterologous C-terminal dimerisation peptide which is a coiled coil domain (such as a leucine zipper from c-fos and c-jun) dimerization peptide, which dimerize, one with the other, and wherein a short flexible linker is between the TCR and the dimerisation domain, and further, wherein a disulfide bond present in the native TCR between the  $\alpha$  and  $\beta$  chains adjacent to the cytoplasmic domain is absent from the recombinant TCR. WO 97/35991 does not teach the TCR complex of instant claims, wherein the disulfide bond between the  $\alpha$  and  $\beta$  chain of the TCR are absent.

Golden et al teach soluble heterodimeric TCR comprising an  $\alpha$  and a  $\beta$  chain, each chain comprising a leucine zipper which dimerizes, one with the other, produced in *E. coli* at yields of 4-5 mg/L (especially Abstract).

O'Shea et al teach heterodimer formation through leucine zippers from c-fos and c-jun (especially Abstract).

Garbozci et al teach a soluble TCR without the interchain disulfide bond present in native TCRs, and that the heterodimerization, refolding and antigenic specificity of the TCR do not require its interchain disulfide bond, transmembrane segments or glycosylation (especially Abstract and page 5408, column 1). Garbozci et al further teach that when  $\alpha$  and  $\beta$  chains expressed without the cysteines that form the interchain disulfide bond were refolded together, they formed heterodimers spontaneously and at higher yields. Garbozci et al teach the yield is routinely 100 mg/ml and the refolded noncovalently associated TCR is stable and very soluble and displays little or no aggregation upon long term storage at 4 degrees C (especially page 5404, column 1, lines 1-14 and page 5407, column 1 at lines 19-22).

Schatz teaches a biotin holoenzyme synthetase encoded by birA, useful for labeling, purification, detection and immobilization of proteins. Schatz teaches fusion proteins comprising polypeptides and the birA sequence for biotinylation at a single specific site (especially abstract and last 2 paragraphs). Schatz teaches biotinylation of a variety of molecules is of practical importance, primarily due to the very tight binding of biotin to the proteins avidin and streptavidin, and that it is advantageous to accomplish biotinylation at a single site using an agent with site specificity (especially paragraph spanning columns 1 and 2 on page 1138).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the soluble heterodimeric TCR of Golden et al, with the Gly-Ser linker of WO 97/35991, as the monomeric TCR in the multimers of WO 97/35991 that were multimerized by avidin and to have produced the proteins in *E. coli* as taught by Golden et al. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made to have used any leucine zipper of appropriate stability such as the leucine zippers from c-fos and c-jun taught by O'Shea et al in the soluble heterodimeric TCR of Golden et al. It would have been prima facie obvious to one

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of ordinary skill in the art at the time the invention was made to have to have a recombinant TCR as taught by the combination of WO 97/35991 and Golden et al without the disulfide bond, as taught by Garboczi et al and further modified as taught by Schatz.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the yield of correctly folded soluble TCR of WO 97/35991 as modified with leucine zippers as taught by Golden et al and O'Shea et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this because Garboczi et al teach that the presence of said bond is not important for heterodimerization and refolding, and further in order to facilitate the production of soluble correctly associated TCR, i.e., in order to insure that disulfide bonds did not form between homologous chains or with other contaminating proteins during purification.

With regard to instant claims 9 and 18, one of ordinary skill in the art at the time the invention was made would have been aware that biotin is the binding partner for avidin, and that biotin would have been incorporated into the monomer TCR in order that the monomer TCR could have been linked via avidin to form multimers and as taught by Schatz. With regard to instant claim 18, one of ordinary skill in the art at the time the invention was made would have been aware that the C-terminus of the heterodimer chain would be the optimal location for biotinylation, rather than at the N-terminus where preservation of antigen binding function was paramount.

Applicant's arguments in the amendment filed 7/28/03 have been fully considered, but are not persuasive.

It is Applicant's position (beginning on page 7 of the said amendment) are of record, briefly, with respect to Garboczi et al that the disulfide bonded long forms of the  $\alpha\beta$  subunits in figure 2a are not relevant to the present application, that the figure 2b results do not demonstrate that the  $\alpha\beta$  subunits form a heterodimer absent the interchain disulfide bond, that figure 3b shows that under reducing conditions on native gel electrophoresis the interchain disulfide bonded  $\alpha\beta$  heterodimer dissociates into its constituent chains and therefore the interchain disulfide bond is necessary for heterodimer formation, that in figure 4 when short forms of  $\alpha\beta$  subunits were electrophoresed under non-reducing or reducing conditions no  $\alpha\beta$  heterodimers were formed, that in figure 5a that an MHC molecule and MHC binding peptide are necessary to stabilize  $\alpha\beta$  heterodimers since no uncomplexed  $\alpha\beta$  heterodimers were present upon native gel electrophoresis under nonreducing conditions and that in figure 5b and 5c no  $\alpha\beta$  heterodimers formed when the short forms of  $\alpha$  and  $\beta$  chains were tested under nonreducing conditions unless there was present an MHC molecule and MHC binding peptide, i.e., that the results taught by Garboczi et al teach that without interchain disulfide bonds,  $\alpha\beta$  subunits do not form heterodimeric TCR except when held in complex with an MHC molecule and an MHC binding peptide. It is Applicant's further position (on page 11 of the said amendment) that Golden et al

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do not show  $\alpha\beta$  TCR that have C-terminal leucine zippers and disulfide linked  $\alpha\beta$  chains are active because Golden et al only teach recognition by TCR-specific antibodies.

It is the Examiner's position that Garboczi et al teach that high yields of correctly folded  $\alpha\beta$  TCR are formed when  $\alpha$  and  $\beta$  chains (short form) made without the cysteine that forms the interchain disulfide bond are refolded and purified. Garboczi et al teach that after refolding, the complexes are subjected to Centriprep-30 concentration, i.e., the TCR (larger than 30,000 Mr) complex preparation was concentrated and size filtered to remove all contaminants and components with molecular weights below 30,000 Mr and that includes the uncomplexed and separate  $\alpha$  and  $\beta$  chains (especially page 5405, column 1 at the section entitled "Refolding the TCR by dilution"). In addition, the TCR was then purified by gel filtration (whereby the TCR complex vs the individual uncomplexed  $\alpha$  and  $\beta$  chains would not elute in the same fraction) and then concentrated in a Centriprep-30 concentrator. Garboczi et al teach that the TCR complexes that are noncovalently associated can bind MHC/peptide with specificity, indicating a correctly folded TCR heterodimer, and that the CTL sister clone 2G4 of A6 which expresses the identical TCR can be functionally engaged by the same MHC/peptide combination with the same specificity as the soluble heterodimer (especially page 5408 at column 1, paragraph 1). Garboczi et al teach native gel shift electrophoresis for demonstrating that the TCR complex could bind to MHC/peptide. Garboczi et al teach « As expected, under nonreducing conditions no disulfide-bonded heterodimer was seen » (especially page 5407, column 1 at lines 8-10), indicating that in with regard to the native gel shift electrophoresis, the noncovalently associated heterodimer was not expected to be observed as a complex, but as separate chains. It is the Examiner's position that the native gel shift electrophoresis assay under nonreducing conditions was used to assess the composition of the heterodimer, i.e., to confirm that the heterodimer was consisted of both  $\alpha$  and  $\beta$  chains and not homodimers of one chain or the other, and to confirm that the TCR was correctly refolded to bind MHC/peptide. The absence of noncovalently associated heterodimer on native gel shift electrophoresis assay under nonreducing conditions is indicative that when the heterodimer is subjected to the nonphysiologic condition of having an electric field applied, the non-covalently associated heterodimer does not migrate as a unit. With regard to Golden et al, it is the Examiner's position that Golden et al teach that their heterodimer can bind to a panel of conformationally sensitive monoclonal antibodies, an indication of correct refolding of the TCR which correlates with functional activity. Applicant is reminded that obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988).

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8. Claims 24 and 25 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99), Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Schatz (Biotechnology, 11, 1993, pages 1138-1143, Applicant's IDS reference in the Form 1449 filed 11/5/99) as applied to claims 1-11, 14-18, 26, 27 and 34-36 supra and further in view of U.S. Patent No. 5,635,363 (Applicant's IDS reference in Form 1449 filed 11/5/99).

WO 97/35991, Golden et al, O'Shea et al, Garboczi et al and Schatz (i.e., "the combined references") have been discussed supra. In addition, WO 97/35991 teaches that the multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses (especially page 10, lines 27-31 and page 11, line 1).

The combined references do not teach a multimeric TCR complex comprising a "detectable label" recited in instant claim 25, nor attached to a "solid structure" recited in instant claim 24.

U.S. Patent No. 5,635,363 discloses soluble MHC/peptide tetramers which are biotinylated and multimerized with streptavidin or with avidin and which further comprise a light detectable label FITC or an enzyme (especially claims) and which further may be bound to an insoluble support such as a bead, i.e., a "solid structure", for the purpose of assay (especially column 8, lines 4-16).

It would have been prima facie obvious to one of ordinary skill at the time the invention was made to have biotinylated, as disclosed by the '363 patent for soluble MHC/peptide tetramers, the soluble TCR complexes taught by the combined references and to have multimerized them using avidin, and further to have labeled them with a detectable label such as is disclosed by the '363 patent for the MHC/peptide tetramers, or to have bound them to a bead, i.e., a solid structure.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to form more avid multimers because the combined references teach the claimed TCR complexes, WO 97/35991 teaches multimers and tetramers and both WO 97/35991 and the '363 patent teach use of avidin for multimerization of heterodimeric proteins, and also because one of ordinary skill in the art at the time the invention was made would have been motivated to facilitate detection because WO 97/35991 teaches that multimeric soluble TCR complexes may be useful in defining the specific peptide/MHC ligands recognized by uncharacterized tumor-specific T cells and T cells involved in autoimmune responses.



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Applicant's arguments in the amendment filed 7/28/03 have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position *supra* with regard to item #7 of this Office Action, apply herein.

9. Claims 1 and 19-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 97/35991 (Applicant's IDS reference in the Form 1449 filed 1/31/00) in view of Golden et al (J. Immunol. Meth., Vol. 206: 163-169, 1997, Applicant's IDS reference in the Form 1449 filed 11/5/99), O'Shea et al (Science, Vol. 245: 646-648, 1989, Applicant's IDS reference in the Form 1449 filed 11/5/99) and Garboczi et al (J. Immunology, Volume 157: 5403-5410, 1996, Applicant's IDS reference in the Form 1449 filed 11/5/99) and further in view of Ahmad et al (Cancer Res., Volume 53: 1484-1488, 1993).

WO 97/35991, Golden et al, O'Shea et al and Garboczi et al (i.e., "the combined references") have been discussed *supra*. The combined references do not teach a multimeric TCR complex attached to a lipid vesicle via derivatised lipid components of the vesicle.

Ahmad et al teach attachment of a biotinylated targeting antibody attached to the surface of a liposome containing biotinylated phosphatidylethanolamine by means of an avidin linker (especially Introduction and Liposome Preparation on page 1484). Ahmad et al further teach that liposomes containing lipid derivatives of polyethylene glycol have circulation times sufficiently long to allow for effective *in vivo* drug delivery.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have attached the multimeric TCR complex taught by the combined references to the liposome of Ahmad et al.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to effectively deliver *in vivo* the multimeric TCR complex taught by the combined references, including WO 97/35991 to be useful for *in vivo* therapy. Claim 23 is included in this rejection because it would also have been *prima facie* obvious to embed the TCR complex in the liposome of Ahmad et al because Ahmad et al teach effective delivery of a substance embedded in the liposome rather than attached to the surface via a derivatized component of the liposome (especially Abstract). Instant claim 24 is included in this rejection because the claim limitation "solid structure" can read on "liposome" of the art reference.

Applicant's arguments in the amendment filed 7/28/03 have been fully considered, but are not persuasive.

Applicant's arguments and Examiner's position *supra* with regard to item #7 of this Office Action, apply herein.

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10. No claim is allowed.

11. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114.

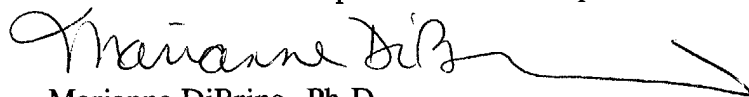
Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 703-308-0061 (after 1/7/04 the telephone number is 571-272-0842). The Examiner can normally be reached on Monday and Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306 (before final) or 703-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Marianne DiBrino, Ph.D.  
Patent Examiner  
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December 7, 2003



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